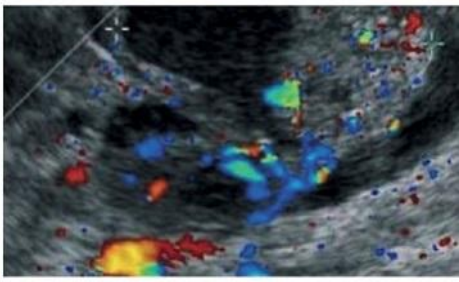
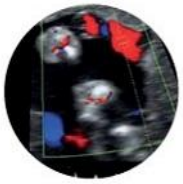
Effect of sildenafil on maternal hemodynamics in pregnancies complicated by severe early-onset fetal growth restriction

ISUOG Education 2020



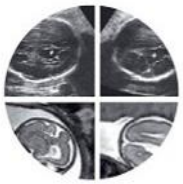
ISUOG delivers quality education courses internationally in Ultrasound in Obstetrics and Gynecology, providing up-to-date research and clinical guidance for a range of topics and professional levels. Our courses are dynamic, interactive and provide delegates with practical tips as well as excellent networking opportunities.



Modern management in twins: All you need to know
4 February 2020
Texas, USA and live streamed worldwide
Course Chairs: Lorraine Dugoff (USA), Asma Khalil (UK), Magda Sanz (USA), Joanne Stone (USA)

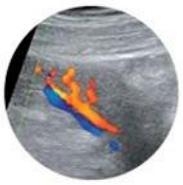
In association with Society for Maternal-Fetal Medicine

Advances in fetal echocardiography
21 - 22 February 2020
London, UK and live streamed worldwide
Course Chairs: Dario Paladini (Italy), Julene Carvalho (UK)



State of the art ultrasound in pregnancy
16 - 18 April 2020
Washington, USA and live streamed worldwide
Course Chairs: Lorraine Dugoff (USA), Aris Papageorghiou (UK), Laurent Salomon (France), Lynn Simpson (USA), Joanne Stone (USA)

In association with Society for Maternal-Fetal Medicine



Doppler and maternal vascular imaging
23 - 24 July 2020
London, UK and live streamed worldwide
Course Chairs: Christoph Lees (UK) and Asma Khalil (UK)

Please note the speakers are subject to change at any time.

ISUOG EDUCATION ISUOG EDUCATION ISUOG EDUCATION ISUOG EDUCATION
isuog.org

Our previous delegates said:

"Very relevant to clinical practice"

"Well organised, good speakers"

"Great course, especially the fact that it was live streamed"

Register now at: isuog.org/events

Discounts available for ISUOG members

Find out more at **isuog.org/events.html**
congress@isuog.org | +44 (0)20 7471 9955

isuog.org

Effect of sildenafil on maternal hemodynamics in pregnancies complicated by severe early-onset fetal growth restriction: planned subgroup analysis from a multicenter randomized placebo-controlled double-blind trial

Asma Khalil[1,2], Andrew Sharp[3], Christine Cornforth[4], Richard Jackson[4], Hatem Mousa[5] Sarah Stock[6], Jane Harrold[4], Mark A. Turner[3], Louise C. Kenny[3], Philip N. Baker[7], Edward D. Johnstone[8], Peter von Dadelszen[9], Laura Magee[9], Aris T. Papageorghiou[1], Zarko Alfirevic[3].

1. Fetal Medicine Unit, St George's Hospital, and St George's, University of London, United Kingdom
2. Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK
3. Department of Women's and Children's Health, University of Liverpool, United Kingdom
4. Liverpool Clinical Trials Unit, University of Liverpool, United Kingdom
5. Fetal Medicine Unit, University of Leicester, United Kingdom
6. The Queen's Medical Research Institute, University of Edinburgh
7. College of Life Sciences, University of Leicester, United Kingdom
8. Maternal & Fetal Health Research Centre, University of Manchester, United Kingdom
9. Department of Women and Children's Health, School of Life Course Sciences, King's College London

Corresponding Author:
Professor Asma Khalil
akhalil@sgul.ac.uk
Vascular Biology Research Centre
Molecular and Clinical Sciences Research Institute
St George's University of London
Fetal Medicine Unit
Department of Obstetrics & Gynaecology
St George's University Hospitals NHS Foundation Trust
Blackshaw Road
London,
United Kingdom
SW17 0QT

Short title: STRIDER cardiovascular

Keywords Fetal growth restriction, sildenafil, cardiovascular; pharmacology; vascular biology; endothelium/vascular type/nitric oxide; hemodynamics

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.20851

CONTRIBUTION

What does this work add to what is already known?

Sildenafil has modest short-term effect on the mother's cardiovascular system. It increases heart rate, reduces blood pressure and arterial stiffness in pregnancies complicated by severe early-onset fetal growth restriction. These changes are consistent with the anticipated vasodilatory effect.

What are the clinical implications of this work?

The findings of this study are valuable in view of the scarcity of available data on the effect of sildenafil on the maternal hemodynamics. They provide reassurance that any cardiovascular changes caused by the administration of sildenafil during pregnancy are modest and appear to have no short or long-term clinical impact on the mother.

ABSTRACT

OBJECTIVES

Fetal growth restriction (FGR) is associated with maternal cardiovascular changes. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitric oxide and has been proposed to alter maternal hemodynamics, potentially improving placental perfusion. Recently, the Dutch trial was stopped prematurely due to excess neonatal mortality secondary to pulmonary hypertension.

The main aim of this study was to investigate the effect of sildenafil on maternal hemodynamics in pregnancies with severe early-onset FGR.

METHODS

In this UK multicenter, placebo-controlled trial, we randomly assigned 135 women with singleton pregnancies and severe early-onset FGR (defined as a combination of estimated fetal weight or abdominal circumference below the 10^{th} centile and absent/reversed end diastolic flow in the umbilical artery on Doppler velocimetry diagnosed between 22^{+0}-29^{+6} weeks' gestation), to receive either sildenafil 25mg three times daily or placebo until 32^{+0} weeks' gestation or delivery.

The maternal blood pressure (BP), heart rate (HR), augmentation index, pulse wave velocity (PWV), cardiac output, stroke volume (SV) and total peripheral resistance were recorded before, 1-2 hours after, and 48-72 hours post-randomization, and 24-48 hours postnatally. For continuous data, the analysis was performed using repeated measures ANOVA methods including terms for time, treatment allocation and their interaction.

RESULTS

Sildenafil increased maternal HR by 4bpm when compared to placebo [5bpm (95%CI: 1, 12) vs 1 (-5, 8); P=0.004] and reduced systolic BP by 1mmHg more than placebo [-4mmHg (-9, 1) vs -3mmHg (-8, 5); P=0.048]. Even after adjusting for maternal BP, sildenafil reduced aortic PWV by 0.6 m/sec more than placebo did [-0.90m/sec (-1.31, -0.51) vs -0.26 (-0.75, 0.59); P=0.001]. Sildenafil was associated with a non-significant decrease in the SV index [-5.5m/m^2/beat (-11, -0.5) vs 0 (-0.5, 4); P=0.056].

CONCLUSIONS

Sildenafil in a dose of 25 mg three times daily increases HR, reduces BP and reduces arterial stiffness in pregnancies complicated by FGR. These changes are modest, consistent with the anticipated vasodilatory effect and their clinical impact on the mother, in both the short- and long-term, remains uncertain.

INTRODUCTION

Early-onset fetal growth restriction (FGR), in the absence of genetic abnormalities or congenital infection, is usually associated with impaired placentation.[1,2] Attempts to develop antenatal therapy have yet to prove successful, so currently the only management option is preterm delivery with its associated significant risks of neonatal mortality and morbidity.

The commonest clinical indication for sildenafil is erectile dysfunction as it causes relaxation of the vascular smooth muscle in the corpus cavernosum that is essential for penile erection. This action is mediated through nitric oxide (NO), which activates guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), reducing intracellular calcium. Sildenafil is a highly selective inhibitor of phosphodiesterase type 5, which is responsible for the degradation of cGMP, ultimately enhancing the effects of NO. NO decreases systemic vascular resistance (SVR) and blood pressure (BP), while nitrates cause a marked reduction in the intensity of early wave reflection in the aorta and improve arterial compliance.[3]

Despite initial promising results from *in vivo* animal studies, and in observational and small randomized controlled human studies,[4-10] sildenafil did not prolong the pregnancy or improve pregnancy outcomes in severe early-onset FGR, when tested in an adequately powered multicenter randomized controlled trial.[11] Recently, the Dutch STRIDER trial was stopped prematurely due to excess neonatal mortality secondary to pulmonary hypertension.[12] Therefore, there is ongoing interest in ascertaining the cardiovascular effects of sildenafil in pregnancy.

Normal pregnancy is associated with marked cardiovascular changes that might limit the additional vasodilator effect of sildenafil on blood vessels which are already maximally dilated. In normal pregnancy, the trophoblast produces NO, a potent venous and arterial

vasodilator. Despite the fact that sildenafil's effect on the cardiovascular system has been investigated in several studies outside pregnancy, little is known about its maternal cardiovascular effects in pregnancy. A recent observational study reported a significant increase in maternal cardiac output (CO) and stroke volume (SV) and a decrease in SVR after two weeks of NO donor therapy.[13] Studies have reported impaired maternal cardiac function and increased arterial stiffness and SVR in pregnancies complicated by FGR.[14-19] In fact, the impaired maternal cardiac output (CO) reported in women who develop hypertensive disorders in pregnancy has recently been shown to be present in those complicated by FGR, but not in those without FGR.[20] Similar changes have been described in non-pregnant individuals with disorders associated with endothelial dysfunction, such as hypertension, coronary heart disease and heart failure.[21-23]

Arterial stiffness is a marker of vascular health and is a prognostic marker for cardiovascular disease in the general population; both low and high risk.[24-27] Both pulse wave velocity (PWV), which is a direct measure of arterial stiffness, and augmentation index (AIx), which is a surrogate measure of arterial stiffness, can be measured non-invasively in pregnancy. We, and others, have demonstrated increased arterial stiffness (PWV and AIx) before, during and after the clinical stage of preeclampsia.[28-36]

The aim of this study was to investigate the effect of sildenafil therapy on maternal cardiovascular parameters in singleton pregnancies complicated by severe early-onset FGR, in a multicenter randomized controlled trial.

METHODS

Trial design and participants

The study was designed as a cardiovascular sub-study within a multicenter randomized controlled trial of sildenafil, prescribed at a dose of 25 mg three times per day, versus the placebo equivalent.[11] This dosage regimen was based on previous studies.[9,37] The inclusion criteria were singleton pregnancies between 22^{+0} and 29^{+6} weeks of gestation with a diagnosis of FGR, where the mothers had agreed to expectant management. FGR was defined as a fetus with abdominal circumference (AC) or estimated fetal weight (EFW) below the 10th centile using local charts, with absent or reversed end diastolic flow in the umbilical artery on Doppler velocimetry. The exclusion criteria included maternal age less than 16 years, known contraindication or allergy to sildenafil, known or suspected significant chromosomal or structural anomaly, reported current cocaine use, or the presence of a condition likely to require delivery within 72 hours (such as severe pre-eclampsia).

Ethical approval was given by the North East Research Ethics Committee (14/NE/0011) in the United Kingdom. Each participating site provided site specific approval and all participants provided written informed consent. The trial was funded by the National Institute for Health Research (NIHR) and the Medical Research Council, neither of which had any direct involvement in study design, data collection, analysis, interpretation or writing the manuscript. The trial was sponsored by the University of Liverpool and Liverpool Women's Hospital. An Independent Safety Data Monitoring Committee (ISDMC) was established to review the safety and efficacy data. The protocol was first registered on 31st July 2014, four months before the first patient was recruited (ISRCTN39133303).

Treatment allocation and trial procedures

A web-based application was used to allocate treatment arm, with randomization stratified by site and gestation. Gestational age was confirmed by first trimester ultrasound assessment of crown-rump length. In each case, the diagnosis of severe early-onset FGR was confirmed by a fetal medicine specialist. In addition, a full history, measurements of maternal cardiovascular parameters (pulse and BP), fetal biometry and Doppler velocimetry were taken, and maternal venepuncture for angiogenic biomarkers was carried out at randomization. Randomization lists were pre-generated using randomly permuted blocks of size 2 and 4.

All participants had a further assessment of BP and pulse, and a blood sample taken within 2 hours after receiving their first oral dose. Subsequently, women were followed up within 3-4 days and at weekly intervals thereafter or earlier when clinically indicated. The rest of clinical care was at the discretion of the local fetal medicine experts and included regular ultrasound assessment of growth and Doppler blood flow, and antenatal cardiotocography.

Medication was over-encapsulated (Sharp Clinical Services, UK) to ensure that the participants, clinicians and pharmacists were blinded to the study drug. All participants received oral medication, sildenafil 25mg or placebo, three times a day. The medication was dispensed in 10 day supplies with a new supply being provided every week to ensure there was no period when medication was missed. Pharmacy logs were used to monitor adherence. The treatment was stopped at 32^{+0} weeks or delivery, whichever came sooner. Women were advised of potential side-effects and their family physician was informed by letter of trial participation.

Data on pregnancy outcomes were collected prospectively from the clinical maternity notes and entered onto an electronic database. Data quality and protocol compliance were monitored regularly using both central and on-site monitoring methods.

Outcome measures

The primary efficacy outcome was the time from randomization until delivery, measured in days. This outcome was chosen as any safe prolongation of pregnancy is likely to be beneficial for the FGR fetus. Secondary outcomes included live birth, fetal and neonatal death, birth weight, neonatal morbidity (any intraventricular hemorrhage, oxygen dependency at 28 days or 36 weeks corrected gestational age, necrotizing enterocolitis or retinopathy of prematurity), use of surfactant, ventilator dependency, admission to neonatal intensive care unit, time to newborn discharge and maternal side-effects.

Maternal cardiovascular assessment

Maternal cardiovascular assessment was performed before randomization, 1-2 hours after randomization, 48-72 hours post-randomization, and 24-48 hours postnatally. The recordings were made by researchers who had received appropriate training on the use of the Arteriograph® and Non-invasive Cardiac Output Monitor (NICOM)®. All measurements were performed in a temperature-controlled room (approximately 22°C) with participants in the semi-recumbent position. The results of the research cardiovascular assessment were not given to the women or their doctors and did not influence subsequent management of the pregnancies.

Recording of maternal BP and heart rate (HR)

The maternal BP and HR were measured by automated devices (3BTO-A2, Microlife®), which were calibrated before and at regular intervals during the study. The women were in the semi-recumbent position, their arms supported at the level of the heart, and a small (<22cm), normal (22 to 32cm), or large (33 to 42cm) adult cuff used depending on the mid-arm circumference was applied.[38] After resting for 5 minutes, BP was measured in both arms simultaneously, and a series of recordings made at one-minute intervals until variations between consecutive readings fell within 10 mmHg in systolic and 6 mmHg in diastolic BP in both arms.[39] When this point of stability was reached, the mean arterial pressure (MAP) of each arm was calculated as the average of the last two stable measurements and, as recommended, the measurement in the arm with the highest final MAP was taken for analysis. The device measured the maternal HR at the same time. The average of the last two measurements was recorded.

Evaluation of the maternal aortic elastic properties and wave reflection indices

Maternal arterial stiffness and wave reflection were assessed using the Arteriograph® (TensioMed Ltd., Budapest, Hungary). The parallel, straight-line distance between the suprasternal notch and the upper border of the symphysis pubis (Jug - Sy) was determined using a caliper as this provides an indirect measure of the aortic length.[40] The Arteriograph® cuff was then applied on the left arm over the brachial artery for estimation of pulse wave velocity (PWV) (m/s) and augmentation index (AIx) (%) and measurement of MAP in mmHg. The cuff acts as a sensor and records the early (direct) systolic wave (P1), late (reflected) systolic wave (P2) and diastolic waves (P3) secondary to the central pressure changes. The Arteriograph® first measures the systolic and diastolic BP oscillometrically. Subsequently, the cuff is decompressed and, in a few seconds, inflated, first to the measured diastolic pressure and second to a supra-systolic pressure (measured SBP plus 35 mmHg). The

pressure fluctuations in the brachial artery at both pressure levels are detected by the cuff and the signals transmitted wirelessly to a computer which contains software (version 1.10.0.1) for analysis. An overview of the cardiovascular parameters recorded in this study is provided as supplementary material.

The AIx was calculated by dividing the pressure difference between the first forward wave due to systole and the second reflected wave (P2-P1) by the pulse pressure (PP) [AIx = (P2 -P1) x 100 / PP] (Figure 1).[41] The aortic PWV (PWV_{Ao}) was calculated by dividing the distance between the suprasternal notch and the upper border of the symphysis pubis in metres (Jug – Sy) by the return time, which is the time interval between the onset of the first systolic wave and the onset of the second reflected wave in seconds (RT).[42]

$$PWVao\left(\frac{m}{s}\right) = \frac{Jug - Sy(m)}{RT / 2(s)}$$

Evaluation of the maternal cardiac output, stroke volume and total peripheral resistance

The maternal CO, SV and total peripheral resistance (TPR) and their indices (CI, SVI and TPRI) were assessed using NICOM® (Cheetah Medical, Portland, OR, USA), a commercially available, non-invasive device which utilizes thoracic bioreactance. Bioreactance technology measures the phase shift in voltage across the thorax. The human thorax can be described in terms of an electric circuit with a capacitor (C) and a resistor (R); together these create thoracic impedance (Zo). The two components of impedance are the amplitude (a) (the magnitude of impedance, which is measured in Ohms (Ω)) and phase (phi, Φ) (the direction of the impedance, measured in degrees). The pulsatile ejection of blood from the heart

modifies the value of R and C, leading to an instantaneous change in the amplitude and phase of Zo. Phase shifts occur due to pulsatile flow, the overwhelming majority of which stems from the aorta. Because the volume of thoracic fluid is relatively static, the NICOM® signal is unaffected by thoracic fluid status including in cases of pulmonary edema. The phase detector within the NICOM® monitor detects the phase shifts and computes these into the NICOM® signal. An explanation of the NICOM® technical aspects and their principals is provided as Supplementary material.

NICOM® is entirely non-invasive and operator independent. The NICOM® system consists of a high frequency (75 kHz) sine wave generator and four dual-electrode skin sensors that are used to establish electrical contact with the patient. Within each sensor, one electrode is used to inject the high-frequency sine wave into the thorax, and the second electrode is used by the voltage input amplifier. Two paired skin sensors are placed on the right side of the thorax and two on the left. The currents are passed between the outer electrodes of the paired skin sensors, whilst the voltages are recorded from the inner pair. The result is a non-invasive CO measurement signal from each half of the body – these are averaged to produce the final CO measurement. The NICOM® system's signal processing unit determines the relative phase shift ($\Delta\ \Phi$) between the input and output signals. The peak rate of change of Φ ($d\Phi/dT_{max}$) is proportional to the peak aortic flow during each heartbeat. The following formula is used to calculate stroke volume: $C \times VET \times d\Phi/dT_{max}$, where C is a constant of proportionality and ventricular ejection time (VET) is determined from the NICOM's® electrocardiographic signals.

Statistical analysis

The STRIDER UK trial recruited 135 women (70 women received sildenafil and 65 placebo) from 18 fetal medicine units in the UK between November 2014 and July 2016. The sample size calculation planned to recruit 112 women; this was later increased to 135 women in consultation with the ISDMC to account for lower than expected live births. Although the power for the primary outcome increased to 94% (post-hoc calculation), this increased sample size would still not have adequate power to detect clinically important differences for most secondary outcomes and the cardiovascular substudy. The participants' groups were defined for analysis on an intention-to-treat basis. None of the women withdrew their consent or were lost to follow-up, so an additional 'per protocol' analysis was not performed.

Data are presented as median and interquartile range (IQR) for continuous data and as n (%) for categorical variables. Comparison between the study groups (sildenafil vs placebo) was by $\chi 2$-test or Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. We analysed the repeat maternal cardiovascular data using repeated measures ANOVA methods including terms for time and treatment allocation. The maternal PWV values were adjusted for BP, while the AIx was adjusted for maternal HR. P values less than 0.05 were considered statistically significant. We performed all analyses with the statistical software package, R (version 3.3.3).

RESULTS

Study population

The STRIDER cardiovascular substudy included 134 women (randomly assigned 69 women to sildenafil and 65 women to placebo) who had recording of the maternal BP and HR at baseline. One-hundred and twenty nine (Sildenafil=66; Placebo=63) women provided data at one hour, 116 women provided data (Sildenafil=62; Placebo=54) 48-72 hours post-randomization, and 65 women provided data (Sildenafil=31; Placebo-34) postnatally. Maternal aortic elastic properties and wave refection indices were performed in 60 women (randomly assigned 32 women to sildenafil and 28 women to placebo), while assessment of the maternal CO, SV and TPR was performed in 83 women (randomly assigned 44 women to sildenafil and 39 women to placebo) (Figure 1). Table 1 presents a comparison between the study groups.

Maternal BP and HR

The maternal systolic BP, diastolic BP and HR values at all time points and by treatment group are illustrated in Figures 2-4. The maternal systolic BP [131.88 (121.75, 138.63) vs 133.75 (124.25, 144.50), p<0.001], diastolic BP [83.50 (77.88, 89.19) vs 87 (80.00, 94.25), p<0.001] and MAP [97.30 (92.65, 105.73) vs 103.0 (94.15, 110.20), p<0.001] values decreased significantly 1-2 hours following the administration of sildenafil. The maternal HR increased significantly 1-2 hours following the administration of sildenafil [83.5 (77.5, 93.5) vs 79.0 (73.0, 87.0), p<0.001]. When compared with pre-randomization, the maternal systolic BP [130.50 (123.50, 142.25) vs 133.75 (124.25, 144.50), p=0.036], diastolic BP

[85.75 (78.50, 90.50) vs 87 (80, 94.25), p=0.045] values were also significantly lower 48-72 hours post-randomization. The maternal HR values were also significantly higher 48-72 hours post-randomization compared to baseline [83.5 (75.1, 92.5) vs 79.0 (73.0, 87.0), p=0.002]. Only the maternal HR values were significantly higher at the postnatal assessment compared to pre-randomization [83.0 (78.8, 91.3) vs 79.0 (73.0, 87.0), p=0.001]. The maternal systolic BP, diastolic BP and HR values before, 1-2 hours after, 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo) are shown in Supplementary Material. Table 2 shows a comparison of the mean difference in the maternal BP and HR between the various time points for the sildenafil and placebo groups. Sildenafil increased maternal HR by 4bpm more than placebo did [5bpm (95% CI: 1, 12) vs 1 (-5, 8); P=0.004] and reduced systolic BP by 1mmHg more than placebo [-4mmHg (-9, 1) vs -3mmHg (-8, 5); P=0.048] (Table 2). There were no significant differences among the remaining values at different time points between the two study groups (p>0.05).

Maternal PWV and AIx

The maternal PWV adjusted for BP, and AIx adjusted for HR values before, 1-2 hours after, 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo) are illustrated in Figures 5 and 6. One to two hours following administration, sildenafil reduced the maternal aortic AIx (AIxAo) adjusted for HR [17.93 (9.06, 28.73) vs 29.34 (12.02, 50.08), p=0.002] and PWV adjusted for MAP [8.85 (8.04, 10.39) vs 10.25 (8.76, 11.27), p<0.001]. When compared with pre-randomization, the maternal AIxAo adjusted for HR [26.67 (12.41, 45.75) vs 29.34 (12.02, 50.08), p=0.001] and PWV adjusted for MAP [8.59 (7.91, 9.75) vs 10.25 (8.76, 11.27), p=0.016] values were also significantly lower 48-72

hours post-randomization. Only the maternal AIxAo adjusted for HR values were significantly lower postnatally when compared to pre-randomization [28.25 (14.36, 44.54) vs 29.34 (12.02, 50.08), p=0.003]. The maternal PWV and AIx values before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo) are shown in Supplementary Material. Table 3 shows a comparison of the mean difference in the maternal PWV and AIxAo between the various time points between the sildenafil and placebo groups. Even after adjusting for maternal BP, sildenafil reduced aortic PWV by 0.6 m/sec more than placebo [-0.90m/sec (-1.31, -0.51) vs -0.26 (-0.75, 0.59); P=0.001]. There were no significant differences among the remaining values at different time points between the two study groups (p>0.05).

Maternal cardiac function and TPR

The maternal CO, SV and TPR before, 1-2 hours after, 48-72 hours post-randomization, and postnatally in the study groups are illustrated in Figures 7-9. Within two hours following administration, sildenafil reduced the maternal SV [66.45 (56.40, 82.94) vs 75.95 (67.05, 84.83), p=0.003] and SVI [41.00 (31.50, 47.00) vs 45.00 (38.00, 51.25), p=0.003]. The maternal CO, CI, SV, SVI, TPR and TPRI values before, 1-2 hours after, 48-72 hours post-randomization, and postnatally in the study groups are shown in Supplementary Material. Table 4 shows a comparison of the mean difference in the maternal CO, CI, SV, SVI, TPR and TPRI between the various time points for the study groups. Sildenafil was associated with a non-significant decrease in the SVI [-5.5m/m2/beat (-11.0, -0.5) vs 0 (-0.5, 4.0); P=0.056]. There were no significant differences among the remaining values at different time points between the two study groups (p>0.05).

DISCUSSION

Summary of the study findings

Our results show that sildenafil reduces maternal BP with a compensatory rise in HR. Even after adjusting for maternal BP and HR, sildenafil reduces arterial stiffness in pregnant women with severe early-onset FGR. However, these effects are mild and short lasting.

Interpretation of the study findings

Our findings of a reduction in BP, increase in HR and decline in arterial stiffness in these pregnant women are consistent with the literature in non-pregnant individuals, despite different regimens of sildenafil, methods of cardiovascular assessment and time points.[43-46]

Taking some correction for p value into account in view of the multiple comparisons, only a slight rise in HR and PWV adjusted for MAP (after 1 - 2 hours) then remain significant. When the cardiovascular parameters were compared between the baseline assessment prior to randomization and post-randomization, some of the changes we observed at the second assessment (within 1-2 hours) were not sustained at the third assessment (48-72 hours). This suggests that the cardiovascular effects of sildenafil in these pregnancies may be short-lived. Other RCTs of sildenafil use in pregnancies complicated by FGR or pre-eclampsia assessed the maternal BP 2-3 hours or within 24 hours after randomization.[47,48] There was no further cardiovascular assessment beyond 24 hours, so their findings could not address whether or not the effect of sildenafil on maternal BP is sustained.[47,48]

Strengths and weaknesses

This is the first RCT which investigates the effect of sildenafil on maternal arterial and cardiac function in pregnancies complicated by severe early-onset FGR. The BP device

used is validated in pregnant women and in pre-eclampsia. The use of a validated device is important as pregnancy-induced vascular changes can affect BP measurements, rendering commonly available devices inaccurate in pregnancies complicated by hypertensive disorders.[49,50] The cardiovascular assessment was performed at several time points, enabling us to assess both the short- and long-term effects of sildenafil. Sildenafil was associated with significant changes in maternal cardiovascular parameters, but these effects were not sustained. All the pregnancies included in this study were complicated by severe early-onset FGR, so we avoided the potentially heterogeneous cardiovascular phenotypes in early and late FGR or in pregnancies complicated by pre-eclampsia (only 17% of our study population had pre-eclampsia).[11] However, our results might not be generalizable to pregnancies with pre-eclampsia or late-onset FGR.

The main limitation of our study is the relatively small number of participants, meaning that the cardiovascular substudy might not have been adequately powered. However, severe early-onset FGR is a rare event affecting less than 1% of pregnancies and most of the RCTs investigating the effect of sildenafil on cardiovascular parameters included smaller numbers of participants than our current study.[43-46]

The availability of non-invasive methods for assessing maternal hemodynamics has enabled researchers to investigate changes in the cardiovascular system in both normal and pathological pregnancies. However, most of these devices are not validated in pregnancy, as validation against the invasive gold standard is challenging for practical and ethical reasons. The devices we used to assess arterial and cardiac function are fully automated, thus minimizing intra- and inter-observer variability. The Arteriograph® has been validated against invasive and non-invasive methods in non-pregnant populations.[41,42,51] Even though there are no direct validation studies of the Arteriograph® in pregnancy, it has been used on

a very large scale in pregnancy research.[17,31,52,53] Measurements from the Arteriograph® had a highly significant correlation with conventional tonometric and piezo-electric platforms.[41] Similarly, there are no published studies of invasive validation of the NICOM® device in pregnant women. However, good agreement between NICOM® and echocardiography has been reported, specifically in the third trimester of pregnancy.[54] Of note, our study findings are consistent with the literature in non-pregnant individuals, despite the use of different methods of cardiovascular assessment.[43-46] Therefore, despite the limitations of our study, the data provide valuable and novel findings.

Clinical and research implications

Our finding of a reduction in BP is consistent with data from RCTs of the use of sildenafil in pregnant women with FGR.[48] In a recent RCT which included 35 singleton pregnancies with FGR between 24 and 31^{+6} weeks of gestation randomized to oral sildenafil citrate, transdermal nitroglycerin (GTN) or placebo, maternal BP decreased with administration of either GTN and sildenafil when recorded 2-3 hours after administration. However, this effect was no longer significant when women with pre-eclampsia were excluded from the analysis.[48]

In normal pregnancy, the trophoblast produces nitric oxide (NO), which is a potent venous and arterial vasodilator that also inhibits platelet aggregation. In pregnancies complicated by pre-eclampsia or IUGR, placental hypoxia and endothelial dysfunction resulting from inflammation are associated with decreased release of NO and increased phosphodiesterase type 5 (PDE-5) activity[4,5]. Therefore, NO donors, which are known PDE-5 inhibitors, have the potential for prevention as well as treatment of IUGR.

Interestingly, our finding of a reduction in BP is also consistent with the data from RCTs of the use of sildenafil in pregnant women with pre-eclampsia.[48] In a recent RCT which included 100 singleton pregnancies with pre-eclampsia between 24 and 33 weeks of gestation randomized to 50mg oral sildenafil citrate every 8 hours or placebo, sildenafil reduced the maternal BP when recorded 24 hours after randomization, when compared with placebo (sildenafil: 100.3±5.6 mm Hg compared with 116.4±5.1 mm Hg, P<0.05; placebo: 110.6±6.2 mm Hg compared with 114.7±6.5 mm Hg, P=0.21).[48] However, recent evidence from animal studies suggests that sildenafil might have different effects on BP depending on the baseline BP.[55] In a recent meta-analysis including 22 animal studies, sildenafil had a significant BP lowering effect only in pregnancies complicated by either FGR or pre-eclampsia (-19 mmHg). The size of the effect was dependent on the baseline BP and there was no effect in the absence of hypertension.[55] This might explain the modest effect of sildenafil seen in our study, as the majority of women in the STRIDER trial did not have hypertension. Of note, none of these RCTs performed detailed maternal cardiovascular assessment, so the effect of sildenafil on maternal PWV, AIx, CO, SV and SVR has not previously been explored.

The findings of our study are valuable in view of the scarcity of available data on the effect of sildenafil on the maternal hemodynamics. They provide reassurance that any cardiovascular changes caused by the administration of sildenafil during pregnancy are modest and appear to have no short or long-term clinical impact on the mother or baby. However, larger studies are needed to ascertain the effect of different doses and frequency of sildenafil administration on maternal hemodynamics and in other populations, such as late-onset FGR.

Conclusions

Sildenafil increases maternal HR and reduces BP and arterial stiffness in pregnancies complicated by severe early-onset FGR. However, these changes are modest and have no short- or long-term clinical impact on the mother.

Acknowledgements: We would like to thank all the women who participated in this study during such a distressing time for them and their families. We would like to thank the members of the Trial Steering Committee (Alan Cameron, Elizabeth Draper, Paul Clarke, Laura Price, Alex Astor, Louise Hardman, and Karen Wilding), Independent Safety and Data Monitoring Committee (Ed Juszczak, Christoph Lees, and Ben Stenson), members of the STRIDER International collaboration, and all the individuals who helped with the management and conduct of the STRIDER UK study. We thank Sarah Quinby and Ediri O'Brien who provided trial management until August, 2016. We are also grateful to Sharp Clinical Services and University of British Columbia (UBC) for supporting the provision of masked investigational medicinal products to research sites and to staff of pharmacy and research and development departments in all of the participating hospitals. We would also like to thank UBC for the development and support of the STRIDER randomization and electronic data capture systems and Liverpool Clinical Laboratories, Royal Liverpool University, and Broadgreen Hospital Trust for doing the Elecsys sFlt-1 and PlGF analyses. STRIDER was funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership, award number 12/62/109. The EME Programme is funded by the MRC and NIHR, with contributions from the Chief Scientist Office in Scotland and National Institute for Social Care and Research in Wales. The trial was sponsored by the University of Liverpool and Liverpool Women's Hospital.

Sources of funding: National Institute for Health Research and Medical Research Council.

Declarations of interest: PNB and LCK report a minority shareholding in Metabolomic Diagnostics, outside of the submitted work, and have patents relating to screening tests (not therapy) for pre-eclampsia issued. All other authors declare no competing interests. This report is independent research funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership. The views expressed in this publication are those of the authors and not necessarily those of the MRC, National Health Service, NIHR, or the Department of Health.

REFERENCES

1. Eastabrook G, Hu Y, von Dadelszen P. The role of decidual natuarl killer cells in normal placentation and in the pathogenesis of preeclampsia. *J Obstet Gynaecol Can* 2008; **30** : 467-476.
2. Trudinger B, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: Clinical significance. *BJOG* 1985; **92** : 23-30.
3. Kelly RP, Gibbs HH, O'Rourke MF, Daley JE, Mang K, Morgan JJ, Avolio AP. Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. *Eur Heart J* 1990; **11** : 138–144.
4. Stanley JL, Andersson IJ, Poudel R, Rueda-Clausen CF, Sibley CP, Davidge ST, Baker PN. Sildenafil citrate rescues fetal growth in the catechol-O-methyl transferase knockout mouse model. *Hypertension* 2012; **59** : 1021-1028.
5. Refuerzo JS, Sokol RJ, Aranda JV, Hallak M, Hotra JW, Kruger M, Sorokin Y. Sildenafil citrate and fetal outcome in pregnant rats. *Fetal Diagn Ther* 2006; **21** : 259-263.
6. Wareing M, Myers JE, O'Hara M, Baker PN. Sildenafil citrate (viagra) enhances vasodilatation in fetal growth restriction. *J Clin Endocrinol Metab* 2005; **90** : 2550-2555.
7. Sánchez-Aparicio P, Mota-Rojas D, Nava-Ocampo AA, Trujillo-Ortega ME, Alfaro-Rodríguez A, Arch E, Alonso-Spilsbury M. Effects of sildenafil on the fetal growth of guinea pigs and their ability to survive induced intrapartum asphyxia. *Am J Obstet Gynaecol* 2008; **198** : 127.e1-127.e6.
8. Wareing M, Myers JE, O'Hara M, Kenny LC, Taggart MJ, Skillern L, Machin I, Baker PN. Phosphodiesterase-5 inhibitors and omental and placental small artery function in normal pregnancy and pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2006; **127** : 41-49.

9. von Dadelszen P, Dwinnell S, Magee LA, Carleton BC, Gruslin A, Lee B, Lim KI, Liston RM, Miller SP, Rurak D, Sherlock RL, Skoll MA, Wareing MM, Baker PN; Research into Advanced Fetal Diagnosis and Therapy (RAFT) Group. Sildenafil citrate therapy for severe early-onset intrauterine growth restriction. *BJOG* 2011; **118** : 624-628.
10. Dastjerdi MV, Hosseini S, Bayani L. Sildenafil citrate and uteroplacental perfusion in fetal growth restriction. *J Res Med Sci* 2012; **17** : 632-636.
11. Sharp A, Cornforth C, Jackson R, Harrold J, Turner MA, Kenny LC, Baker PN, Johnstone ED, Khalil A, von Dadelszen P, Papageorghiou AT, Alfirevic Z; STRIDER group. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2018; **2** : 93-102.
12. Hawkes Nigel. Trial of Viagra for fetal growth restriction is halted after baby deaths. *BMJ* 2018; 362:k3247.
13. Tiralongo GM, Pisani I, Vasapollo B, Khalil A, Thilaganathan B, Valensise H. Effect of a nitric oxide donor on maternal hemodynamics in fetal growth restriction. *Ultrasound Obstet Gynecol* 2018 ; **51** : 514-518.
14. Bamfo JE, Kametas NA, Turan O, Khaw A, Nicolaides KH. Maternal cardiac function in fetal growth restriction. *BJOG* 2006; **113** : 784-791.
15. Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, Cherney DZ, Hladunewich MA. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. *Circulation* 2010; **122** : 1846-1853.

16. Guy GP, Ling HZ, Machuca M, Poon LC, Nicolaides KH. Maternal cardiac function at 35-37 weeks' gestation: relationship with birth weight. *Ultrasound Obstet Gynecol* 2017; **49** : 67-72.
17. Khalil A, Sodre D, Syngelaki A, Akolekar R, Nicolaides KH. Maternal hemodynamics at 11-13 weeks of gestation in pregnancies delivering small for gestational age neonates. *Fetal Diagn Ther* 2012; **32** : 231-238.
18. Vasapollo B, Valensise H, Novelli GP, Altomare F, Galante A, Arduini D. Abnormal maternal cardiac function precedes the clinical manifestation of fetal growth restriction. *Ultrasound Obstet Gynecol* 2004; **24** : 23-29.
19. Vasapollo B, Valensise H, Novelli GP, Larciprete G, Di Pierro G, Altomare F, Casalino B, Galante A, Arduini D. Abnormal maternal cardiac function and morphology in pregnancies complicated by intrauterine fetal growth restriction. *Ultrasound Obstet Gynecol* 2002; **20** : 452-457.
20. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, Lees CC. Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. *Am J Obstet Gynecol* 2018; **218** : 517.
21. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37** : 1236-1241.
22. Ohtsuka S, Kakihana M, Watanabe H, Sugishita Y. Chronically decreased aortic distensibility causes deterioration of coronary perfusion during increased left ventricular contraction. *J Am Coll Cardiol* 1994; **24** : 1406-1414.

23. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieère P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 1997; **30** : 1410-1415.

24. Terai M, Ohishi M, Ito N, Takagi T, Tatara Y, Kaibe M, Komai N, Rakugi H, Ogihara T. Comparison of arterial functional evaluations as a predictor of cardiovascular events in hypertensive patients: the Non-Invasive Atherosclerotic Evaluation in Hypertension (NOAH) study. Hypertens Res 2008; 31:1135–1145.

25. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier Hl; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27:2588-2605.

26. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A, Health ABC Study. Elevated Aortic Pulse Wave Velocity, a Marker of Arterial Stiffness, Predicts Cardiovascular Events in Well-Functioning Older Adults. Circulation 2005; 111:3384-3390. doi:10.1161/CIRCULATIONAHA.104.483628.

27. O'Rourke MF. Arterial pressure waveforms in hypertension. Minerva Med 2003; 94:229-250.

28. Khalil A, Jauniaux E, Harrington K. Antihypertensive Therapy and Central Hemodynamics in Women With Hypertensive Disorders in Pregnancy. Obstet Gynecol 2009; 113:646-654.

29. Khalil AA, Cooper DJ, Harrington KF. Pulse wave analysis: a preliminary study of a novel technique for the prediction of pre-eclampsia. BJOG 2009; 116:268-76; discussion 276-277.

30. Khalil A, Cowans NJ, Spencer K, Goichman S, Meiri H, Harrington K. First-trimester markers for the prediction of pre-eclampsia in women with a-priori high risk. Ultrasound Obstet Gynecol 2010; 35:671-679.
31. Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal hemodynamics at 11-13 weeks' gestation and risk of pre-eclampsia. Ultrasound Obstet Gynecol 2012; 40:28-34.
32. Hausvater A, Giannone T, Sandoval Y-HG, Doonan RJ, Antonopoulos CN, Matsoukis IL, Petridou ET, Daskalopoulou SS. The association between preeclampsia and arterial stiffness. J Hypertens 2012; 30:17-33.
33. Franz MB, Burgmann M, Neubauer A, Zeisler H, Sanani R, Gottsauner-Wolf M, Schiessl B, Andreas M. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. Acta Obstet Gynecol Scand 2013; 92:960-966.
34. Namugowa A, Iputo J, Wandabwa J, Meeme A, Buga GAB. Comparison of arterial stiffness in preeclamptic and normotensive pregnant women from a semi-rural region of South Africa. Clin Exp Hypertens 2017; 39:277-283.
35. Foo FL, McEniery CM, Lees C, Khalil A; International Working Group on Maternal Hemodynamics. Assessment of arterial function in pregnancy: recommendations of the International Working Group on Maternal Hemodynamics. Ultrasound Obstet Gynecol 2017; 50:324-331.
36. Osman MW, Nath M, Breslin E, Khalil A, Webb DR, Robinson TG, Mousa HA. Association between arterial stiffness and wave reflection with subsequent development of placental-mediated diseases during pregnancy: findings of a systematic review and meta-analysis. J Hypertens 2018; 36:1005-1014.

37. Samangaya RA, Mires G, Shennan A, Skillern L, Howe D, McLeod A, Baker PN. A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. *Hypertens Pregnancy* 2009; **28** : 369-382.
38. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; **45** : 142–161.
39. National Heart Foundation of Australia. Hypertension management guide for doctors 2004. Available at: http://www.heartfoundation.org.au. Accessed April 1, 2009.
40. Sugawara J, Hayashi K, Yokoi T, Tanaka H. Age-associated elongation of the ascending aorta in adults. *J Am Coll Cardiol Img* 2008; **1** : 739–748.
41. Baulmann J, Schillings U, Rickert S, Uen S, Dusing R, Illyes M, Cziraki A, Nickering G, Mengden T. A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods. *J Hypertens* 2008; **26** :523–528.
42. Horváth IG, Németh A, Lenkey Z, Alessandri N, Tufano F, Kis P, Gaszner B, Cziráki A. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. *Hypertens* 2010; **28** : 2068-2075.

43. Hirata K, Adji A, Vlachopoulos C, O'Rourke MF. Effect of sildenafil on cardiac performance in patients with heart failure. *Am J Cardiol* 2005; **96** : 1436-1440
44. Vlachopoulos C, Hirata K, O'Rourke MF. Effect of sildenafil on arterial stiffness and wave reflection. *Vasc Med* 2003; **8** : 243-248.
45. Schofield RS, Edwards DG, Schuler BT, Estrada J, Aranda JM, Pauly DF, Hill JA, Aggarwal R, Nichols WW. Vascular effects of sildenafil in hypertensive cardiac transplant recipients. *Am J Hypertens* 2003; **16** : 874-877.
46. Mahmud A, Hennessy M, Feely J. Effect of sildenafil on blood pressure and arterial wave reflection in treated hypertensive men. *J Hum Hypertens* 2001; **15** : 707-713.
47. Trapani A Jr, Gonçalves LF, Trapani TF, Vieira S, Pires M, Pires MM. Perinatal and Hemodynamic Evaluation of Sildenafil Citrate for Preeclampsia Treatment: A Randomized Controlled Trial. *Obstet Gynecol* 2016; **128** : 253-259.
48. Trapani A Jr, Gonçalves LF, Trapani TF, Franco MJ, Galluzzo RN, Pires MM. Comparison between transdermal nitroglycerin and sildenafil citrate in intrauterine growth restriction: effects on uterine, umbilical and fetal middle cerebral artery pulsatility indices. *Ultrasound Obstet Gynecol* 2016; **48** : 61-65.
49. Reinders A, Cuckson AC, Jones CR, Poet R, O'Sullivan G, Shennan AH. Validation of the Welch Allyn 'Vital Signs' blood pressure measurement device in pregnancy and pre-eclampsia. *BJOG* 2003; **110** : 134-138.
50. Natarajan P, Shennan AH, Penny J, Halligan AW, de Swiet M, Anthony J. Comparison of auscultatory and oscillometric automated blood pressure monitors in the setting of preeclampsia. *Am J Obstet Gynecol* 1999; **181** : 1203-1210.
51. Ne´meth Zs, Mo´ cza´ r K, Dea´k Gy. Evaluation of the Tensioday ambulatory blood pressure monitor according to the protocols of the British Hypertension Society and the

Association for the Advancement of Medical Instrumentation. *Blood Pressure Monit* 2002; **7** : 191–197.

52. Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal Hemodynamics in Normal Pregnancies at 11–13 Weeks' Gestation. *Fetal Diagn Ther* 2012; **32** : 179–185.
53. Khalil A, Garcia-Mandujano R, Chiriac R, Akolekar R, Nicolaides KH. Maternal Hemodynamics at 11–13 Weeks' Gestation in Gestational Diabetes Mellitus. *Fetal Diagn Ther* 2012; **31** : 216-220.
54. Vinayagam D, Patey O, Thilaganathan B, Khalil A. Cardiac output assessment in pregnancy: comparison of two automated monitors with echocardiography. *Ultrasound Obstet Gynecol* 2017; **49** : 32-38.
55. Paauw ND, Terstappen F, Ganzevoort W, Joles JA, Gremmels H, Lely AT. Sildenafil During Pregnancy: A Preclinical Meta-Analysis on Fetal Growth and Maternal Blood Pressure. *Hypertension* 2017; **70** : 998-1006.

FIGURE LEGENDS

Figure 1. Study Flow chart.

Figure 2. Maternal brachial systolic blood pressure (BP) values before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). In the sildenafil group, the maternal systolic BP [131.88 (121.75, 138.63) vs 133.75 (124.25, 144.50), p<0.001] values decreased significantly 1-2 hours following the administration of sildenafil. When compared with pre-randomization, the maternal systolic BP [130.50 (123.50, 142.25) vs 133.75 (124.25, 144.50), p=0.036], diastolic BP [85.75 (78.50, 90.50) vs 87 (80, 94.25), p=0.045] values were also significantly lower 48-72 hours post-randomization. The maternal systolic BP values were not significantly different in the postnatal period when compared with pre-randomization values (p>0.05). * indicates p<0.05 when compared with the pre-randomization values. Values in red belong to the sildenafil group, while values in blue belong to the placebo group.

Figure 3. Maternal brachial diastolic blood pressure (BP) values before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). In the sildenafil group, the maternal diastolic BP [83.50 (77.88, 89.19) vs 87 (80.00, 94.25), p<0.001] values decreased significantly 1-2 hourd following the administration of sildenafil. When compared with pre-randomization, the maternal diastolic BP [85.75 (78.50, 90.50) vs 87 (80, 94.25), p=0.045] values were also significantly lower 48-72 hours post-randomization. The maternal diastolic BP were not significantly different in the postnatal period when compared with pre-randomization values (p>0.05). * indicates p<0.05 when

compared with the pre-randomization values. Values in red belong to the sildenafil group, while values in blue belong to the placebo group.

Figure 4. Maternal heart rate (HR) values before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). In the sildenafil group, the maternal HR increased significantly 1-2 hours following the administration of sildenafil [83.5 (77.5, 93.5) vs 79.0 (73.0, 87.0), p<0.001]. The maternal HR values were also significantly higher 48-72 hours post-randomization compared to baseline [83.5 (75.1, 92.5) vs 79.0 (73.0, 87.0), p=0.002]. The maternal HR values were significantly higher at the postnatal assessment compared to pre-randomization [83.0 (78.8, 91.3) vs 79.0 (73.0, 87.0), p=0.001]. In the placebco group, the maternal HR values were significantly higher at the postnatal assessment compared to pre-randomization [87 (70, 94.5) vs 76 (70, 85.5), p=0.025]. * indicates p<0.05 when compared with the pre-randomization values. Values in red belong to the sildenafil group, while values in blue belong to the placebo group.

Figure 5. Maternal pulse wave velocity (PWV) values adjusted for blood pressure (BP) before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). Within 1-2 hours following administration, sildenafil reduced the maternal PWV adjusted for MAP [8.85 (8.04, 10.39) vs 10.25 (8.76, 11.27), p<0.001]. When compared with pre-randomization, the maternal PWV adjusted for MAP [8.59 (7.91, 9.75) vs 10.25 (8.76, 11.27), p=0.016] values were also significantly lower 48-72 hours post-randomization. The values were not significantly different postnatally when compared to pre-randomization (p>0.05). * indicates p<0.05 when compared with the pre-randomization

values. Values in red belong to the sildenafil group, while values in blue belong to the placebo group.

Figure 6. Maternal aortic augmentation index (AIxAo) values adjusted for heart rate before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). One to two hours following administration, sildenafil reduced the maternal aortic AIx (AIxAo) adjusted for HR [17.93 (9.06, 28.73) vs 29.34 (12.02, 50.08), p=0.002]. When compared with pre-randomization, the maternal AIxAo adjusted for HR [26.67 (12.41, 45.75) vs 29.34 (12.02, 50.08), p=0.001] values were also significantly lower 48-72 hours post-randomization. The maternal AIxAo adjusted for HR values were significantly lower postnatally when compared to pre-randomization [28.25 (14.36, 44.54) vs 29.34 (12.02, 50.08), p=0.003]. * indicates $p<0.05$ when compared with the pre-randomization values. Values in red belong to the sildenafil group, while values in blue belong to the placebo group.

Figure 7. Maternal cardiac output (CO) values before, one hour after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). When compared with pre-randomization, the maternal CO values were not significantly different at 1-2 hours post-randomization, 48-72 hours post-randomization, or postnatally ($p>0.05$ for all).

Figure 8. Maternal stroke volume values before, one hour after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). One to two hours following administration, sildenafil reduced the maternal SV [66.45 (56.40, 82.94) vs 75.95 (67.05, 84.83), p=0.003]. When compared with pre-randomization, the maternal SV values were not significantly different at 48-72 hours post-randomization or postnatally ($p>0.05$ for

all). * indicates $p<0.05$ when compared with the pre-randomization values. Values in red belong to the sildenafil group, while values in blue belong to the placebo group.

Figure 9. Maternal total peripheral resistance values (TPR) before, 1-2 hours after, and 48-72 hours post-randomization, and postnatally in the study groups (sildenafil and placebo). When compared with pre-randomization, the maternal TPR values were not significantly different at 1-2 hours post-randomization, 48-72 hours post-randomization, or postnatally ($p>0.05$ for all).

Table 1. Baseline characteristics

Covariate	**Level**	**Placebo (n=65)**	**Sildenafil (n=69)**	**Total (n=134)**
Gestation at Delivery in weeks	median (IQR)	28.43 (27.29, 30.14)	28.14 (26.71, 29.71)	28.29 (26.86, 29.71)
Maternal age in years	median (IQR)	33 (28, 36)	29 (26, 34)	30 (27, 35)
Maternal weight in kilograms	median (IQR)	70 (60, 82)	66 (58, 80)	69.5 (60, 82)
Maternal height in cm	median (IQR)	163 (158, 166)	163 (158, 167)	163 (158, 166.75)
Maternal BMI (kg/m^2)	median (IQR)	26.49 (22.72, 31.22)	24.8 (22.86, 31.23)	25.42 (22.785, 31.22)
Ethnicity	African	7 (54%)	6 (46%)	13
	Asian - Other	0 (0%)	1 (100%)	1
	Caribbean	2 (50%)	2 (50%)	4
	Chinese	1 (100%)	0 (0%)	1
	Indian	3 (43%)	4 (57%)	7

Covariate	Level	Placebo (n=65)	Sildenafil (n=69)	Total (n=134)
	Latin American/Hispanic	0 (0%)	1 (100%)	1
	Other	1 (33%)	2 (67%)	3
	Pakistani	8 (57%)	6 (43%)	14
	White - British	35 (45%)	43 (55%)	78
	White - European	5 (71%)	2 (29%)	7
	White - Other	2 (100%)	0 (0%)	2
	White and Asian	0 (0%)	1 (100%)	1
	White and Black African	0 (0%)	1 (100%)	1
	White and Black Caribbean	1 (100%)	0 (0%)	1
Gestational Hypertension	No	42 (42%)	58 (58%)	100
	Yes	23 (68%)	11 (32%)	34

Covariate	**Level**	**Placebo (n=65)**	**Sildenafil (n=69)**	**Total (n=134)**
Pre-eclampsia	No	54 (49%)	56 (51%)	110
	Yes	11 (46%)	13 (54%)	24
Gestational Diabetes	No	62 (48%)	67 (52%)	129
	Yes	3 (60%)	2 (40%)	5
Smoking Status	Current smoker	2 (15%)	11 (85%)	13
	Non-smoker at conception	57 (53%)	51 (47%)	108
	Stopped after 15+0 weeks	3 (60%)	2 (40%)	5
	Stopped by 15+0 weeks	3 (38%)	5 (62%)	8
Estimated fetal weight	median (IQR)	436 (326, 594)	448 (352, 616.75)	444 (344, 613)
Gestation at recruitment in weeks	median (IQR)	25.571 (24.143, 27.429)	25.143 (24, 27.571)	25.357 (24, 27.536)

Covariate	**Level**	**Placebo (n=65)**	**Sildenafil (n=69)**	**Total (n=134)**
Previous pregnancy	No	40 (53%)	35 (47%)	75
	Yes	25 (42%)	34 (58%)	59
Birthweight in grams	> 500	21 (44%)	27 (56%)	48
	≤ 500	36 (52%)	33 (48%)	69

Table 2. Comparison of the mean difference in the maternal blood pressure (BP) and heart rate (HR) between the various time points for the sildenafil and placebo groups.

Time Points	**Factor**	**Placebo (n=62)**	**Sildenafil (n=65)**	**P value**
Pre vs Post Randomization (1 - 2hr)	Maternal right arm systolic BP (mmHg)	-2.00 (-8.75, 4.50)	-5.50 (-10.50, 4.38)	0.086
	Maternal left arm systolic BP (mmHg)	-2.50 (-8.50, 6.50)	-3.00 (-8.25, 1.50)	0.082
	Maternal right arm diastolic BP (mmHg)	-1.50 (-6.25, 3.50)	-4.50 (-8.88, 1.00)	0.029
	Maternal left arm diastolic BP (mmHg)	-2.00 (-6.75, 3.00)	-4.00 (-9.25, -1.00)	0.192
	Maternal right arm MAP (mmHg)	-1.80 (-6.63, 3.08)	-3.85 (-9.28, 1.06)	0.028
	Maternal left arm MAP (mmHg)	-1.65 (-6.65, 3.00)	-3.70 (-7.85, 0)	0.125

Time Points	Factor	Placebo (n=62)	Sildenafil (n=65)	P value
	Maternal HR (bpm)	1.25 (-5.38, 7.88)	5.00 (1.00, 12.00)	0.004
	Maternal average systolic BP	-2.75 (-7.50, 5.25)	-4.13 (-9.94, 1.44)	0.048
	Maternal average diastolic BP	-1.50 (-5.63, 2.38)	-4.75 (-8.56, -0.31)	0.089
Pre vs Post Randomization (48 - 72hr)	Maternal average (between the 2 readings) Right arm systolic BP (mmHg)	-2.00 (-10.50, 3.38)	-3.25 (-8.88, 2.88)	0.602
	Maternal average (between the 2 readings) Left arm systolic BP (mmHg)	-0.50 (-8.25, 9.50)	-4.00 (-7.25, 4.00)	0.670
	Maternal average (between the 2 readings) Right arm	-0.75 (-6.50, 6.25)	-2.25 (-5.88, 1.50)	0.714

Time Points	Factor	Placebo (n=62)	Sildenafil (n=65)	P value
	diastolic BP (mmHg)			
	Maternal average (between the 2 readings) Left arm diastolic BP (mmHg)	1.50 (-7.00, 5.38)	-2.50 (-6.75, 4.25)	0.370
	Maternal average (between the 2 readings) Right arm MAP (mmHg)	-1.00 (-8.00, 5.16)	-3.25 (-6.35, 3.10)	0.991
	Maternal average (between the 2 readings) Left arm MAP (mmHg)	0.33 (-7.35, 6.03)	-1.70 (-6.78, 3.08)	0.344
	Maternal HR (bpm)	0.50 (-5.00, 6.50)	5.00 (-1.38, 10.38)	0.13
	Maternal average systolic BP	-1.63 (-8.63, 5.94)	-3.00 (-8.75, 5.25)	0.961

Time Points	Factor	Placebo (n=62)	Sildenafil (n=65)	P value
	Maternal average diastolic BP	-0.5.00 (-5.50, 5.69)	-2.00 (-5.75, 3.25)	0.332
Pre vs Postnatal	Maternal average (between the 2 readings) Right arm systolic BP (mmHg)	-2.75 (-13.00, 8.25)	-2.50 (-18.25, 2.75)	0.217
	Maternal average (between the 2 readings) Left arm systolic BP (mmHg)	-1.50 (-11.00, 6.50)	0 (-12.50, 6.50)	0.444
	Maternal average (between the 2 readings) Right arm diastolic BP (mmHg)	0.25 (-7.88, 7.50)	-2.50 (-10.75, 5.50)	0.496
	Maternal average (between the 2 readings) Left arm diastolic BP (mmHg)	-1.00 (-8.50, 10.50)	-2.00 (-13.00, 4.50)	0.199

Time Points	Factor	Placebo (n=62)	Sildenafil (n=65)	P value
	Maternal average (between the 2 readings) Right arm mean arterial pressure (MAP) (mmHg)	-1.08 (-9.85, 7.30)	-1.50 (-14.10, 3.75)	0.337
	Maternal average (between the 2 readings) Left arm MAP (mmHg)	-1.85 (-9.15, 8.00)	-1.15 (-15.65, 5.00)	0.176
	Maternal heart rate (bpm)	6.00 (-1.00, 12.00)	8.50 (1.25, 12.00)	0.506
	Maternal average systolic BP	-0.50 (-10.88, 8.06)	-1.50 (-13.25, 3.00)	0.238
	Maternal average diastolic BP	0.75 (-6.94, 8.81)	-2.50 (-9.75, 5.25)	0.194
Post Randomization (48hr	Maternal average (between the 2 readings) Right arm	-0.75 (-6.13, 5.88)	-4.25 (-13.25, 8.38)	0.615

Time Points	Factor	Placebo (n=62)	Sildenafil (n=65)	P value
– 72hr) vs Postnatal	systolic BP (mmHg)			
	Maternal average (between the 2 readings) Left arm systolic BP (mmHg)	-0.50 (-9.00, 4.75)	0.75 (-10.50, 7.50)	0.816
	Maternal average (between the 2 readings) Right arm diastolic BP (mmHg)	2.75 (-11.63, 6.50)	0.75 (-7.25, 7.50)	0.611
	Maternal average (between the 2 readings) Left arm diastolic BP (mmHg)	2.50 (-4.25, 5.75)	1.50 (-10.63, 6.00)	0.582
	Maternal average (between the 2 readings) Right arm MAP (mmHg)	0.90 (-9.28, 6.13)	0 (-9.59, 8.76)	0.915
	Maternal average (between the 2 readings) Left arm	0.85 (-7.68, 4.88)	1.50 (-10.54, 3.89)	0.643

Time Points	Factor	Placebo (n=62)	Sildenafil (n=65)	P value
	MAP (mmHg)			
	Maternal HR (bpm)	4.75 (-3.25, 19.25)	1.50 (-6.88, 6.75)	0.241
	Maternal average systolic BP	-1.38 (-7.00, 6.19)	-2.25 (-11.19, 8.50)	0.686
	Maternal average diastolic BP	4.25 (-8.94, 7.31)	1.88 (-7.38, 5.38)	0.971

Table 3. Comparison of the mean difference in the maternal aortic augmentation index (AIxAo) and pulse wave velocity (PWV) between the various time points for the sildenafil and placebo groups.

Time Point	**Factor**	**Placebo (n=28)**	**Sildenafil (n=30)**	**P value**
Pre vs Post Randomization (1 - 2hr)	AIxAo (%)	-4.50 (-10.28, 2.93)	-5.85 (-17.10, 2.23)	0.937
	Aortic PWV (m/s)	0.25 (-0.37, 0.90)	-0.05 (-0.55, 0.83)	0.565
	AIxAo adjusted for heart rate (%)	-6.03 (-15.52, 3.45)	-10.21 (-27.55, -2.86)	0.516
	Aortic PWV (m/s) adjusted for MAP	-0.26 (-0.75, 0.59)	-0.90 (-1.31, -0.51)	0.001
	Factor	**Placebo (n=21)**	**Sildenafil (n=27)**	**P value**
Pre vs Post Randomization (48 - 72hr)	AIxAo (%)	-4.20 (-8.53, 1.00)	-1.00 (-10.20, 4.70)	0.599
	Aortic PWV (m/s)	0 (-0.65, 0.78)	-0.21 (-1.20, 0.30)	0.538

Time Point	**Factor**	**Placebo (n=28)**	**Sildenafil (n=30)**	**P value**
	AlxAo adjusted for heart rate (%)	0 (-3.22, 1.87)	-1.20 (-3.08, -0.41)	0.269
	Aortic PWV (m/s) adjusted for MAP	-0.45 (-2.23, 1.55)	-0.83 (-1.96, 0.20)	0.489
	Factor	**Placebo (n=12)**	**Sildenafil (n=12)**	**P value**
Pre vs Postnatal	AlxAo (%)	3.30 (-2.00, 18.71)	7.30 (-15.90, 10.70)	0.231
	Aortic PWV (m/s)	0.10 (-1.00, 1.10)	0.50 (-0.30, 1.30)	0.800
	AlxAo adjusted for heart rate (%)	-0.32 (-0.91, 0.91)	-1.25 (-4.73, -0.58)	0.189
	Aortic PWV (m/s) adjusted for MAP	0.01 (-1.71, 1.29)	0.31 (-0.61, 0.58)	0.793

Time Point	**Factor**	**Placebo (n=28)**	**Sildenafil (n=30)**	**P value**
	Factor	**Placebo (n=7)**	**Sildenafil (n=12)**	**P value**
Post Randomization (48hr – 72hr) vs Postnatal	AlxAo (%)	4.20 (-11.10, 16.10)	6.00 (5.77, 19.30)	0.676
	Aortic PWV (m/s)	1.00 (0.20, 1.70)	-0.60 (-1.30, 1.02)	0.508
	AlxAo adjusted for heart rate (%)	-0.70 (-2.55, -0.11)	0 (-0.33, 1.08)	0.771
	Aortic PWV (m/s) adjusted for MAP	0.43 (-0.67, 1.86)	-0.49 (-1.32, 1.76)	0.405

Table 4. Comparison of the mean difference in the maternal cardiac function and total peripheral resistance between the various time points for the sildenafil and placebo groups.

Time Point	**Factor**	**Placebo (n=36)**	**Sildenafil (n=42)**	**P value**
Pre vs Post Randomization (1 - 2hr)	Cardiac Output (CO) (L/min)	0.20 (-0.50, 0.90)	0 (-0.75, 0.58)	0.467
	Cardiac Index (CI)	0.05 (-0.30, 0.50)	0.10 (-0.48, 0.20)	0.226
	Heart Rate (HR)	3.00 (-2.00, 8.00)	8.00 (2.50, 14.00)	0.025
	Stroke volume (SV) (ml)	0.40 (-7.20, 8.10)	-8.15 (-14.68, 0.43)	0.855
	Stroke volume index (SVI)	0 (-5.00, 4.00)	-5.50 (-11.00, -0.50)	0.056

Time Point	Factor	Placebo (n=36)	Sildenafil (n=42)	P value
	Total peripheral resistance (TPR)	-56.00 (-280.00, 108.00)	-19.50 (-154.25, 134.00)	0.533
	Total peripheral resistance index (TPRI)	-127.00 (-550.00, 211.00)	-38.50 (-288.25, 239.25)	0.270
	Factor	**Placebo (n=31)**	**Sildenafil (n=39)**	**P value**
Pre vs Post Randomization (48 - 72hr)	Cardiac Output (CO) (L/min)	0.30 (-0.30, 1.45)	0 (-0.55, 0.45)	0.232
	Cardiac Index (CI)	0.20 (-0.20, 0.90)	0 (-0.30, 0.15)	0.103
	Heart Rate (HR)	1.0 (-5.0, 7.5)	8.0 (-1.5, 12.5)	0.443
	Stroke volume (SV) (ml)	9.30 (-3.95, 14.65)	-1.60 (-13.30, 8.20)	0.581

Time Point	Factor	Placebo (n=36)	Sildenafil (n=42)	P value
	Stroke volume index (SVI)	3.50 (-2.00, 8.25)	-1.00 (-8.50, 4.00)	0.041
	Total peripheral resistance (TPR)	-133.50 (-366.00, 149.00)	-36.00 (-199.50, 102.50)	0.073
	Total peripheral resistance index (TPRI)	-263.00 (-690.00, 302.00)	-57.00 (-373.50, 170.00)	0.117
	Factor	**Placebo (N=18)**	**Sildenafil (N=18)**	**P value**
Pre vs Postnatal	CO (L/min)	0.55 (-0.38, 1.63)	0.35 (0, 1.05)	0.636
	CI	0.30 (-0.18, 0.95)	0.10 (0, 0.70)	0.626
	HR	5.0 (1.5, 13.5)	13.0 (2.5, 15.0)	0.175
	SV (ml)	-4.9 (-18.98, 8.00)	-8.10 (-13.23, 2.60)	0.381

Time Point	Factor	Placebo (n=36)	Sildenafil (n=42)	P value
	SVI	-0.50 (-5.75, 4.75)	-4.00 (-6.00, 6.00)	0.252
	TPR	-2.50 (-235.50, 233.75)	-43.00 (-145.00, 81.25)	0.557
	TPRI	-2.50 (-425.25, 379.25)	-65.00 (-448.50, 133.75)	0.534
	Factor	**Placebo (n=14)**	**Sildenafil (n=17)**	**P value**
Post Randomization (48hr – 72hr) vs Postnatal	CO (L/min)	0.10 (-0.73, 0.85)	0.10 (-1.10, 1.70)	0.861
	CI	-0.05 (-0.40, 0.48)	0 (-0.70, 0.90)	0.734
	HR	7.00 (0.25, 12.50)	4.00 (-3.00, 11.00)	0.169

Time Point	Factor	Placebo (n=36)	Sildenafil (n=42)	P value
	SV (ml)	-14.20 (-24.50, 0.70)	-6.20 (-14.70, 12.60)	0.056
	SVI	-2.50 (-7.75, 2.50)	-3.00 (-8.00, 7.00)	0.365
	TPR	-58.00 (-308.25, 326.25)	-46.00 (-174.00, 275.00)	0.517
	TPRI	-50.00 (-630.50, 509.25)	-96.00 (-333.00, 498.00)	0.596

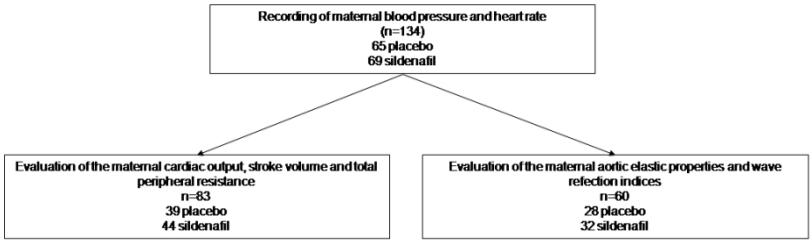


Figure 1

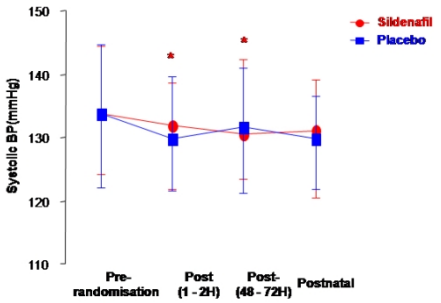


Figure 2

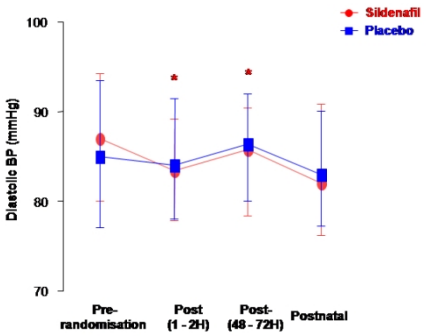


Figure 3

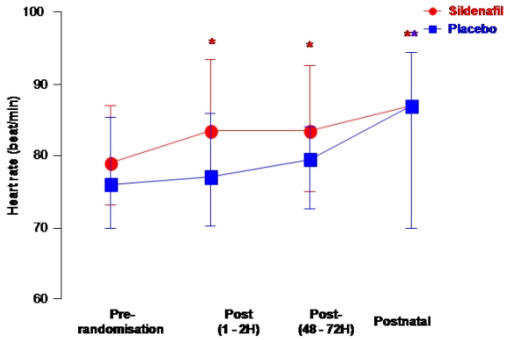


Figure 4

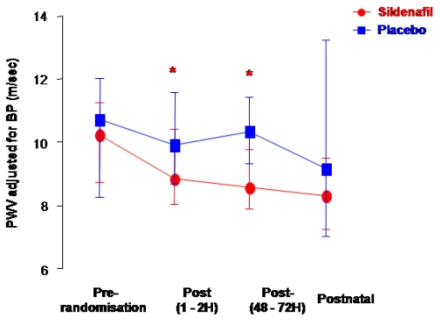


Figure 5

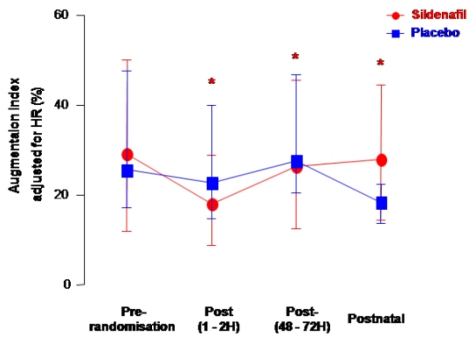


Figure 6

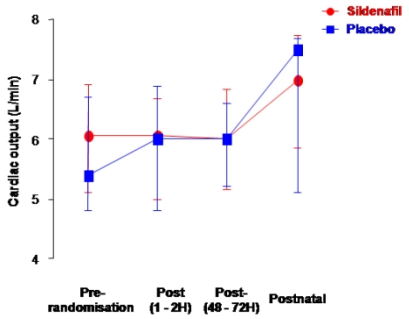


Figure 7

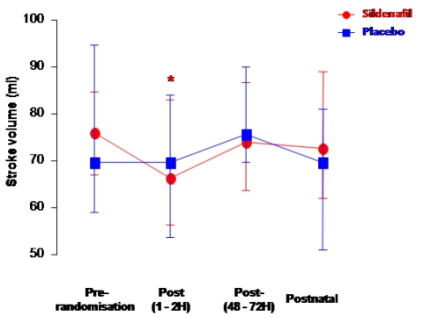


Figure 8

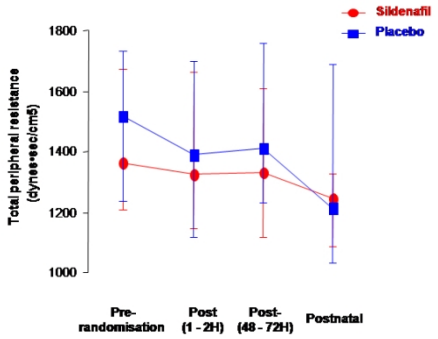


Figure 9